Appl. Serial No. : 10/621,803
Submission under 37 C.F.R. § 1.114 dated August 31, 2005
Reply to Office Action of July 5, 2005

REMARKS

Applicant acknowledges receipt of the Office Action mailed July 5, 2005.

All of the amendments to the claims are supported by the application, as originally filed. The term "amplification primer" has been substituted in place of "oligonucleotide primer" in Claim 1 because the latter term finds explicit definition in the Specification on page 9 at line 19. The recitation of "a first amplification primer that comprises..." in Claim 1 provides a convenient means for referring to a particular immobilized primer that is useful for amplifying the target nucleic acid. This amendment is supported, for example, by the Specification which instructs, beginning on page 13 at line 11 and extending to page 14 at line 20, that a composite array comprises: (1) a solid support, such as a bead or multiwell plate; (2) at least one species of primer; and (3) at least one species of hybridization probe. The word, "samples" was introduced into the claims in the previous Response because it appears under the definition of "array" on page 8 of the Specification, and because "array" was introduced into the claims as a way of addressing the spatial arrangement of probes in relation to primers in one embodiment of the invention. The word "samples" has been deleted from Claim 1 because it is unnecessary in view of the deletion of the word "array," and has been replaced by the word "species." Support for this amendment can be found, for example, in the Specification on page 12 at line 10. Deletion of "in an array" from Claim 1 is appropriate because the utility of the phrase in defining the spatial arrangement of immobilized probes and primers is superceded by the newly added "wherein" clause which addresses the distribution of immobilized oligonucleotides.

Indeed, certain amendments to the claims particularly address the structural arrangement of immobilized oligonucleotides on the surface of the recited solid support. The phrase, "each of said plurality of samples of labeled hybridization probes in said array being spatially separated from the others, but not spatially separated from said field of immobilized primers," have been deleted and replaced by a "wherein" clause specifying that "no portion of said surface of said solid

support is excluded from occupation by an immobilized oligonucleotide...." Support for the amendment can be found in the Specification on page 11 at line 21, where it is stated, "[t]he oligonucleotides or other biomolecules may be attached to surfaces in discrete spots on planar surfaces that characterize microarrays, or over dispersed areas on particulates or planar surfaces." The Specification on page 14 at lines 10-20 goes on to describe how it is desirable for sites on the solid support surface that are not occupied by bonds to the immobilized hybridization probes to be occupied by bonds to oligonucleotide primers to result in a substantially uniform distribution of primers over the surface of the device. The Specification on page 14 at line 29 describes how oligonucleotide primers conveniently may be immobilized to the solid support surface of a probe array by immersion in a liquid composition includes the oligonucleotides that are to be immobilized. The Specification on page 15 at line 4, in describing device manufacture states, "[i]t is unnecessary to exclude from contact with the primer-containing composition any part of the probe array occupied by immobilized probe molecules." Working Example 9 describes construction of a device for amplifying and detecting nucleic acids by a process involving immersion of an arrayed surface in a composition comprising immobilizable primers "so that primers immobilized uniformly over the available plastic surface of the well" in a multiwell plate (*see* page 47 at lines 23-30). In this instance, the inner bottom surface of a well in a multiwell plate was first derivatized completely (according to the method of Example 5) to facilitate covalent coupling, then coupled with molecular beacon hybridization probes in an array format, and then the completely contacted with a solution containing the amplification primer to be immobilized. Clearly, no portion of the surface of the solid support of the instantly disclosed device was excluded from occupation by an immobilized oligonucleotide.

The language of dependent Claims 3-7 and 9 have been conformed to the amendment of Claim 1. Additionally, Claim 7 has been amended to specify that the recited hybridization probes comprise a fluorophore moiety and a quencher moiety. Support for the amendment can be found in the Specification beginning on page 19 at line 15, and extending to page 21 at line 12.

Other amendments have been made to enhance readability of the claims, and are considered non-substantive. For example, "at least one..." has been replace by "a plurality of..." in the language of Claim 1 related to description of the immobilized primer. This change simplifies subsequent reference to the immobilized primers. The recitation of "wherein" before each of three clauses at the end of Claim 1 is similarly regarded as a non-substantive amendment. Other minor amendments merely conform the language of the claims.

New Claims 32-43 also find support in the Specification. Claims 32 and 35 are supported by the disclosure appearing in the paragraph bridging pages 12-13, which illustrates a device having only two species of arrayed probes and a single species of immobilized primer. Claims 33 and 34 are supported by the disclosure appearing in Example 9, which describes a composite array having replicate spots of a single probe species and one species of immobilized primer. Claim 36 is supported by the disclosure appearing on page 13 at lines 11-14, which discusses that the solid support can be a bead; and by the disclosure appearing on page 16 at lines 9-17, which discusses alternative array formats. Claims 39-43 are supported by the disclosure in working Examples 7-9. Example 9 particularly illustrates a reaction mixture wherein the surface of the solid support comprises immobilized probes and primers. The make-up of the the "liquid composition" elements of Claims 39-43 is disclosed generally in Examples 7-9. A definition of "fluid communication" can be found on page 9 at lines 25-30.

Applicant notes that the "fluid communication" limitation recited in new Claim 39 actually goes opposite the instruction provided by the Brennan reference cited in the most recent Office Action. Where the instant claims require fluid communication among each immobilized primer and probe on the surface of the solid support, Brennan teaches the opposite. More specifically, Brennan teaches array structures comprising patterned hydrophilic and hydrophobic sites (page 19 at line 16), and that hydrophobic portions of the structure maintain physical separation between individual reactions on the derivatized surface (*see* Brennan starting on page 20 at line 33 and extending to page 21 at line 2; and on page 24 at lines 15-18).

Claims 1, 3-7, 9 and 19 have been amended. Claim 8 has been canceled. Claims 1-7, 9, 19 and 32-43 will be pending following entry of this Amendment. No new matter is being added by the amendments made herein.

Entry of this Response is respectfully requested.

The Rejection Under § 102(b)

Claims 1-9 have been rejected under 35 U.S.C. § 102(b) as anticipated by a published PCT Application naming Brennan et al., as inventors ("Brennan" hereafter). The Office Action indicated that certain terms recited in the claims were not particularly defined in the Specification, and so examination was conducted by interpreting those terms broadly. More specifically, the examination was carried out by construing the phrase, "immobilized substantially uniformly over said surface," as covering *any form of immobilization of nucleic acids over the surface*, and by construing the phrase, "within the field of immobilized primers," as covering *any spatial relationship between the immobilized probes and primers* (*see* Office Action at page 2, items 5-6). The Examiner concluded that the previously pending claims embraced a prior art reference that described a platform for conducting large numbers of amplification reactions. The claims have now been amended to claim the invention more particularly, while avoiding the prior art.

I. Brennan Requires Portions of the Surface of the Solid Support to be Excluded from Occupation by Immobilized Oligonucleotides

The present invention is not anticipated by Brennan because the amended claims recite structural features which are neither taught nor suggested by the reference. While Brennen outlines on page 7 an amplifying and detecting system that comprises probes and primers immobilized on "derivatized" areas of a solid support surface, the meaning of this term, and the scope of the disclosed amplifying and detecting system, must be considered in the context of the

teaching of the reference. When this is done, it becomes apparent that the presently claimed invention does not embrace the device taught by the prior art.

Indeed, the instant claims recite structural features which actually go opposite the teaching of the Brennan reference. More specifically, Claim 1 has been amended to recite, "wherein no portion of said surface of said solid support is excluded from occupation by an immobilized oligonucleotide, said device having been manufactured by a process comprising immersion of said surface in a liquid composition comprising immobilizable oligonucleotide primers." This feature of the instant invention conflicts with the content of the Brennan reference, which instructs (*see* first paragraph under Summary, page 4) methods and apparatus "for performing a large number of reactions using array assembly." The only structures taught for practicing the disclosed method are "surface tension arrays" (page 5 at line 12), which "comprise patterned hydrophilic and hydrophobic sites" (page 19 at line 16). Referring to surface tension arrays, Brennan instructs that (page 19 at line 23) "a hydrophilic site is spatially segregated from neighboring hydrophilic sites because of the hydrophobic sites between hydrophilic sites." Brennen further instructs that the "*hydrophilic sites are derivatized sites*" (page 21 at line 3), and that the hydrophobic sites serve to maintain spatial separation between different reactions taking place in contact with the surface of the solid support (*see* page 20 at line 33; page 19 at line 31). The physical arrangement of reactant-containing hydrophilic sites and hydrophobic sites is illustrated in Figure 2, and chemical derivatization and photomasking techniques that can be used to create patterned distributions of hydrophobic and hydrophilic areas are discussed, for example, on page 21 at line 10 and extending to page 22 at line 9. Thus, it should be clear that the hydrophobic areas of the arrays disclosed by Brennan are essential to the operation thereof, and that these areas are excluded from occupation by immobilized oligonucleotides. This goes opposite the instant claims, which require that no portion of the surface is excluded from occupation by immobilized oligonucleotides.

Since the amended claims require that "no portion of said surface of said solid support is

excluded from occupation by an immobilized oligonucleotide...," and since this goes opposite the instruction provided by Brennan, which teaches immobilized oligonucleotides independently confined to hydrophilic sites separated by hydrobphobic areas to ensure spatial separation between different reactions being conducted on a surface, the claims cannot be anticipated by the prior art. Since the amended claims are not anticipated by the prior art, withdrawal of the rejection under § 102(b) is appropriate.

The Rejection Under § 103(a)

Claim 19 has been rejected under 35 U.S.C. § 103(a) as being obvious in view of the combined disclosure of the above-discussed Brennan reference, a published PCT application naming Hu et al., as inventors ("Hu" hereafter), and a section from a 1988 Stratagene Catalog.

Claim 19, drawn to a kit comprising a device in accordance with amended Claim 1, cannot be considered obvious over the cited combination of references because the primary reference actually leads away from creation of the presently claimed device for the reasons given above. More specifically, It would not have been obvious for one of ordinary skill in the art to have consulted the Brennan reference, learned about techniques for independently disposing probes and primers on hydrophilic areas of a solid support, each hydrophilic area being separated from the other by a hydrophobic region devoid of immobilized oligonucleotides, and then proceed opposite that teaching by immobilizing probe and primer oligonucleotides over an entire surface of the solid support. Indeed, failing to maintain separation among independent sets of immobilized probes and primers would result in undesirable mixing of reagents, and would defeat the instruction provided by Brennan regarding (*see* first paragraph under Summary, page 4) methods and apparatus "for performing a large number of reactions using array assembly."

Since the primary reference does not teach or suggest the device structure specified by amended Claim 1, and since neither Hu nor the Stratagene Catalog provides supplemental

instruction that would result in the claimed device, the device of Claim 1 must be considered nonobvious in light of the prior art. It follows that any kit incorporating the nonobvious device also must be considered nonobvious in light of the cited references. Accordingly, withdrawal of the rejection under § 103(a) is appropriate.

CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the telephone number shown below.

Deposit Account Information

No fees are believed due in connection with this filing. If this is in error, please charge any fees due in connection with this Reply to Deposit Account No. 07-0835 in the name of Gen-Probe Incorporated.

Certificate of Transmission

I hereby certify that this correspondence (and any referred to as attached) is being sent by facsimile to (571) 273-8300 on the date indicated below to Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Respectfully submitted,
GEN-PROBE INCORPORATED

Dated: August 31, 2005

By: _____

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